Inventors: Liu, et al. Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 2

CLAIMS

1. (currently amended) A compound of Formula I:

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R¹ is a member selected from the group consisting of H, C₆-C₁₀ aryl substituted with 0-3 R^{1a}, or a 5- to 6-membered monocyclic or 8- to 10-membered bicyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R^{1a}, a C₃-C₈ cycloalkyl substituted with 0-2 R^{1b}, wherein said C₃-C₈ cycloalkyl is saturated or unsaturated; and a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R^{1e} and is saturated or unsaturated;

each R^{1a} is independently a member selected from the group consisting of H, C_1 - C_3 perfluoroalkyl, C_3 - C_7 cycloalkyl, F, Cl, Br, CN, NO₂, OR^{10} , SCH_3 , $S(=O)CH_3$, $S(=O)_2R^{10}$, $NR^{11}R^{12}$, acetyl, $C(=O)OR^{13}$, $C(=O)NR^{13}R^{14}$, $S(=O)_2NR^{13}R^{14}$, phenyl substituted with 0-3 R^{15} , a 5- to 6 membered monocyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} , a C_3 - C_8 heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R^{16} and is saturated or unsaturated, and a C_1 - C_4 alkyl substituted with 0-2 R^{16} ;

each R^{1b} is independently a member selected from the group consisting of H, OH, F, Cl, acetyl, =O, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃ and OCF₃;

each R^{1e} -is independently a member selected from the group consisting of H, OH, F, CI, =O, C₁-C₆-alkyl substituted with 0-2 R^{16} , C₁-C₆-alkoxy, CF₃, OCF₃, C(=O) R^{10} , S(=O) $_2R^{10}$, tBoc, Cbz; phenyl substituted with 0-3 R^{15} ; a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group eonsisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} ;

Inventors: Liu, et al. Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 3

 R^2 is a member selected from the group consisting of a phenyl substituted with 0-3 R^{15} , a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{45} , a C_1 - C_6 alkyl substituted with 0-2 R^{2a} , wherein said C_1 - C_6 alkyl optionally contains a heteroatom selected from the group consisting of -O-, -S-, and -S(=O)₂-, a C_2 - C_6 alkenyl, a C_2 - C_6 alkynyl, a C_3 - C_7 cycloalkyl substituted with 0-2 R^{19} , wherein said C_3 - C_7 cycloalkyl optionally contains a heteroatom selected from C_7 - C_7 - C_7 - and a C_7 - C_{11} bicycloalkyl substituted with 0-2 R^{19} ;

each R^{2a} is independently a member selected from the group consisting of a C_6 - C_{10} aryl substituted with 0-3 R^{15} , a 5- to 6-membered monocyclic or 8- to 10-membered bicyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R^{15} , a C_3 - C_8 cycloalkyl substituted with 0-2 R^{19} , and a C_7 - C_{11} bicycloalkyl substituted with 0-2 R^{19} ;

 R^3 is a member selected from the group consisting of H and C_1 - C_4 alkyl; subscript n is 0 or 1;

R⁴ is a member selected from the group consisting of H and C₁-C₆ alkyl; alternatively, R² and R⁴ are taken together to form a C₅-C₇-cycloalkyl substituted with 0-2 R¹⁹;

 R^5 is a member selected from the group consisting of H, C_3 - C_7 cycloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkyne, phenyl substituted with 0-2 R^{15} ; 5—to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} , and a C_1 - C_6 alkyl substituted with 0-2 R^{18} , wherein said C_1 - C_6 alkyl optionally contains a heteroatom selected from the group consisting of $-O_7$, $-S_7$, $-S(=O)_2$ - and $-NR^{17}$ -;

Y is a member independently selected from the group consisting of a bond and $-(CR^{20}R^{21})_m$ -W- $(CR^{22}R^{23})_p$ -;

subscript p is 1 or 2;

subscript m is 0 or 1;

W is a member independently selected from the group consisting of a bond, -O-, -S-, -S(=O)-, -S(=O)₂- and -NR 12 -;

X is selected from the group consisting of -C(=O)-, -OC(=O)-, $-NR^{24}C(=O)$ - and $-S(=O)_2$ -;

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 4

each of R^6 , R^7 , R^8 and R^9 is independently a member selected from the group consisting of H and C_1 - C_4 alkyl;

alternatively, R^5 and R^7 are taken together to form a C_5 C_7 cycloalkyl substituted with $0.2 R^{19}$;

alternatively, R⁵ and R⁹ are taken together to form a 6-7 membered heterocyclic ring containing 1-2 heteroatoms each independently a member selected from the group consisting of N, O and S;

Ar is a member selected from the group consisting of phenyl substituted with 0-3 R^{29} , and 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R^{29} :

each R¹⁰ is independently a member selected from the group consisting of H, C₃-C₇ cycloalkyl, a C₁-C₃ perfluoroalkyl, a C₁-C₄ alkyl substituted with 0-1 R²⁵, and a phenyl substituted with 0-3 R¹⁵; a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R¹⁵, and a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R¹⁶;

each R¹¹ is independently a member selected from the group consisting of H, 'BOC, Cbz, C₃-C₈ cycloalkyl, (C₁-C₆ alkyl)-C(=O)-, (C₁-C₆ alkyl)-S(=O)₂- and a C₁-C₆ alkyl; each of R¹², R¹³ and R¹⁴ is independently a member selected from the group consisting of H and C₁-C₄ alkyl;

alternatively, R¹³-and R¹⁴-on the same N atom are taken together to form a C₅-C₇ heterocycle containing 1-2 heteroatoms each independently a member selected from the group consisting of N, O and S;

each R^{15} is independently a member selected from the group consisting of H, OH, F, Cl, Br, I, CN, NO₂, COOR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴, acetyl, -SCH₃, -S(=O)CH₃, -S(=O)₂CH₃, NR²⁶R²⁷, C₁-C₆ alkoxy, C₁-C₃ perfluoroalkyl, C₁-C₃ perfluoroalkoxy and a C₁-C₆ alkyl;

each R^{16} is independently a member selected from the group consisting of H, OH, $COOR^{13}$, $C(=O)NR^{13}R^{14}$, $S(=O)_2NR^{13}R^{14}$, acetyl, $-SCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, C_1-C_6 alkoxy, $NR^{26}R^{27}$, and a phenyl substituted with 0-3 R^{15} , a.5 to 6 membered heteroaryl

Inventors: Liu, et al.

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 5

containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R¹⁵, and a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R¹⁵ and is saturated or unsaturated;

R¹⁷ is a member selected from the group consisting of H and C₁-C₄ alkyl;

each R^{18} is independently a member selected from the group consisting of H, OH, F, Cl, CN, NO₂, C(=O)OR³⁰, C(=O)NR¹³R¹⁴, NR¹¹R¹², a C₁-C₃ perfluoroalkyl, a C₁-C₃ perfluoroalkoxy, a phenyl substituted with 0-3 R¹⁵, a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R¹⁵ and is saturated or unsaturated; and C₃-C₈ cycloalkyl;

each R^{19} is a independently a member selected from the group consisting of C_1 - C_4 alkyl, F, Cl and C_1 - C_4 alkoxy, CF_3 and OCF_3 ;

alternatively, two R^{19} on the same carbon may be combined to form C_3 - C_6 eyeloalkyl; each of R^{20} , R^{21} , R^{22} and R^{23} is independently a member selected from the group consisting of a bond, H, F, OH, C_1 - C_4 alkyl, and C_1 - C_3 alkylhydroxy;

alternatively, R^{20} -and R^{21} -or R^{22} -and R^{23} -are taken together to form a C_3 - C_6 eyeloalkyl;

R²⁴ is a member selected from the group consisting of H and C₁-C₄ alkyl;

each R²⁵ is independently a member selected from the group consisting of H, C₃-C₇ cycloalkyl, a phenyl substituted with 0-3 R¹⁵ and a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said 5- to 6-membered heteroaryl is substituted with 0-2 R¹⁵;

each R^{26} is independently a member selected from the group consisting of H, C_1 - C_4 alkyl, $(C_1$ - C_4 alkyl)-C(=O)- and $(C_1$ - C_4 alkyl)-S(=O)2-;

each R^{27} is independently a member selected from the group consisting of H and C_1 - C_4 alkyl;

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 6

alternatively, R²⁶ and R²⁷ on the same N atom are taken together to form a C₅-C₇ heterocycle containing 1-2 heteroatoms each independently a member selected from the group consisting of N, O and S;

each R²⁸ is independently a member selected from the group consisting of H, a C₁-C₆ alkyl, C₃-C₈ cycloalkyl, a phenyl substituted with 0-3 R¹⁵, a benzyl substituted with 0-2 R¹⁵; each R²⁹ is independently a member selected from the group consisting of H, F, Cl, Br, I, CN, NO₂, OR²⁸, SR²⁸, S(=O)R²⁸, S(=O)₂R²⁸, S(=O)₂NR¹³R¹⁴, NR²⁶R²⁷, acetyl, C(=O)NR¹³R¹⁴, C(=O)OR¹³, C₁-C₆ alkyl, OCHF₂, SCF₃, OCF₃, and -C(=NH)NH₂, and 5-to 6-membered heteroaryl containing 1 to 4-heteroatoms each independently a member selected from the group consisting of N, O and S;

alternatively, two R²⁹-substituted on adjacent atoms may be combined to form a 5 to 6 membered heterocyclic fused radical, wherein said 5 to 6 membered heterocyclic fused radical comprise 1 or 2 heteroatom(s) selected from O, S and N; wherein said 5 to 6 membered heterocyclic fused radical is substituted with 0.1 oxo;

alternatively, R^{29} and R^9 are taken together to form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s) each independently a member selected from the group consisting of N, O and S; wherein said 5 to 7 membered fused heterocyclic ring is substituted with 0-2 R^{19} ;

each R^{30} is independently a member selected from the group consisting of H, C_3 - C_7 cycloalkyl, C_1 - C_4 alkyl substituted with 0-1 R^{25} , and a phenyl substituted with 0-3 R^{15} , and a 5-to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R^{15} :

and with the proviso that R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are not all hydrogen.

2-3. (canceled)

4. (currently amended) The compound of claim 1, wherein÷ R^1 is a member selected from the group consisting of phenyl substituted with 0-3 R^{1a} , furanyl substituted with 0-3 R^{1a} , C₃ C₆ cycloalkyl substituted with 0-3 R^{1a} , indolyl substituted with 0-3 R^{1a} , or 6-membered heterocyclyl substituted with 0-3 R^{1a} , pyidazinyl substituted with 0-3 R^{1a} ; imadazolyl-substituted with 0-3 R^{1a} , thicallyl substituted

Inventors: Liu, et al.

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 7

with 0-3 R^{1a}, oxadiazolyl substituted with 0-3 R^{1a}, pyrazolyl substituted with 0-3 R^{1a}, isoxazolyl substituted with 0-3 R^{1a}, oxazolyl substituted with 0-3 R^{1a}, and pyridyl substituted with 0-3 R^{1a}.

5-6. (canceled)

7. (currently amended) The compound of claim 1, according to formula Ia:

wherein:

R¹ is a member selected from the group consisting of a C₃-C₈ cycloalkyl substituted with 0-2 R^{1b}, wherein said C₃-C₈ cycloalkyl is saturated or unsaturated and a C₄-C₇ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R^{1e} and is saturated or unsaturated;

 R^2 is a member selected from the group consisting of a phenyl substituted with 0-3 R^{15} , a 5- to 6-membered monocyclic heteroaryl containing 1-to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{45} , a C_1 - C_6 alkyl substituted with 0-2 R^{2a} , and a C_3 - C_7 cycloalkyl substituted with 0-2 R^{19} ; and

Ar is phenyl substituted with 0-3 R²⁹, or alternatively, R²⁹ and R⁹ are taken together to form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s) each independently a member selected from the group consisting of N, O and S; wherein said 5- to 7-membered fused heterocyclic ring is substituted with 0-2 R¹⁹.

8. (currently amended) The compound of claim 7, wherein:

 R^2 is a member selected from the group consisting of a C_1 - C_2 alkyl substituted with 1 R^{2a} , and C_1 - C_6 alkyl;

each R^{2a} is independently a member selected from the group consisting of a phenyl substituted with 0-3 R^{15} , and a C_3 - C_8 cycloalkyl substituted with 0-2 R^{19} ;

Inventors: Liu, et al. Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 8

 R^5 is a member selected from the group consisting of H, C_3 - C_7 cycloalkyl; a C_1 - C_6 alkyl substituted with 0-1 R^{18} , wherein said C_1 - C_6 alkyl optionally contains a heteroatom selected from the group consisting of $-O_7$, $-S_7$, $-S(=O)_7$, and $-NR^{17}$ -; and

each R^{18} is independently a member selected from the group consisting of H, OH, F, Cl, CN, C(=O)OR³⁰, C(=O)NR¹³R¹⁴, NR¹¹R¹², a phenyl substituted with 0-3 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R¹⁵ and is saturated or unsaturated; and C₃-C₈ cycloalkyl.

9. (original) The compound of claim 7, wherein said compound is of the formula:

10. (currently amended) The compound of claim 1, according to formula Ic:

wherein:

 R^{1} is a member selected from the group consisting of tBu, phenyl substituted with 0-2 R^{15} , a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} , and a C_4 - C_7 -heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R^{16} ;

each R^{1e} is independently a member selected from the group consisting of H, OH, F, CI, =O, C₁-C₆ alkyl substituted with 0-2 R¹⁶, a C₁-C₆ alkoxy, CF₃, OCF₃, C(=O)R¹⁰, S(=O)₂R¹⁰, tBoc, Cbz, phenyl substituted with 0-3 R¹⁵, and a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R¹⁵;

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 9

Y is a member independently selected from the group consisting of a bond and $-(CR^{20}R^{21})_m$ -W- $(CR^{22}R^{23})_p$ -, wherein m is 0, W is a bond, and $R^{22}R^{23}$ are both H;

 R^2 is a member selected from the group consisting of a phenyl substituted with 0-3 R^{15} , a 5- to 6-membered monocyclic heteroaryl containing 1 to 4-heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} , a C_1 - C_6 -alkyl-, a C_1 - C_3 alkyl substituted with 1 R^{2a} , and a C_3 - C_7 cycloalkyl substituted with 0-2 R^{19} ;

each R^{2a} is independently a member selected from the group consisting of a C_6 - C_{10} aryl substituted with 0-3 R^{15} , a 5- to 6-membered monocyclic or 8- to 10-membered bicyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R^{15} , a C_3 - C_8 cycloalkyl substituted with 0-2 R^{19} , and a C_7 - C_{11} bicycloalkyl substituted with 0-2 R^{19} ; and

Ar is phenyl substituted with 0-3 R²⁹, or alternatively, R²⁹ and R⁹ are taken together to form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s) each independently a member selected from the group consisting of N, O and S; wherein said 5- to 7-membered fused heterocyclic ring is substituted with 0-2 R¹⁹.

11. (currently amended) The compound of claim 10, wherein:

 R^2 is a member selected from the group consisting of a C_1 - C_2 alkyl substituted with 1 R^{2a} , and C_1 - C_6 alkyl;

each R^{2a} is independently a member selected from the group consisting of a phenyl substituted with 0-3 R^{15} , and a C_3 - C_8 cycloalkyl substituted with 0-2 R^{19} ;

 R^5 is a member selected from the group consisting of H, C_3 - C_7 cycloalkyl; a C_1 - C_6 alkyl substituted with 0-1 R^{18} , wherein said C_1 - C_6 alkyl optionally contains a heteroatom selected from the group consisting of $-O_7$, $-S_7$, $-S_7$, $-S_7$, $-S_7$, and $-S_7$, and

each R^{18} is independently a member selected from the group consisting of H, OH, F, Cl, CN, C(=O)OR³⁰, C(=O)NR¹³R¹⁴, NR¹¹R¹², a phenyl substituted with 0-3 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R¹⁵ and is saturated or unsaturated; and C₃-C₈ cycloalkyl.

Inventors: Liu, et al.

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 10

12. (currently amended) The compound of claim 10, wherein said compound is of the formula:

13. (currently amended) The compound of claim 1, according to formula Id:

wherein:

R¹ is a member selected from the group consisting of methyl, benzyl, C₆-C₁₀ aryl substituted with 0-3 R^{1a}, and a 5- to 6-membered monocyclic or 8- to 10-membered bicyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R^{1a};

each R^{1a} is independently a member selected from the group consisting of H, C_1 - C_3 perfluoroalkyl, C_3 - C_7 cycloalkyl, F, Cl, Br, CN, NO₂, OR¹⁰, SCH₃, S(=O)CH₃, S(=O)₂R¹⁰, NR¹¹R¹², acetyl, C(=O)OR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴, and phenyl substituted with 0-3 R¹⁵, a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R¹⁵; and a C_4 - C_4 -alkyl; and

Ar is phenyl substituted with 0-3 R²⁹, or alternatively, R²⁹ and R⁹ are taken together to form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s) each independently a member selected from the group consisting of N, O and S; wherein said 5- to 7-membered fused heterocyclic ring is substituted with 0-2 R¹⁹.

14. (currently amended) The compound of claim 13, wherein:

 R^2 is a member selected from the group consisting of a C_1 - C_2 alkyl substituted with 1 R^{2a} , and C_1 - C_6 alkyl;

each R^{2a} is independently a member selected from the group consisting of a phenyl substituted with 0-3 R^{15} , and a C_3 - C_8 cycloalkyl substituted with 0-2 R^{19} ;

Inventors: Liu, et al. Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 11

 R^5 is a member selected from the group consisting of H, C_3 - C_7 cycloalkyl; a C_1 - C_6 alkyl substituted with 0-1 R^{18} , wherein said C_1 - C_6 alkyl optionally contains a heteroatom selected from the group consisting of -O-, -S-, -S(=O)-, -S(=O)₂- and -NR¹⁷-; and

each R^{18} is independently a member selected from the group consisting of H, OH, F, Cl, CN, C(=O)OR³⁰, C(=O)NR¹³R¹⁴, NR¹¹R¹², a phenyl substituted with 0-3 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R¹⁵ and is saturated or unsaturated; and C₃-C₈ cycloalkyl.

15. (original) The compound of claim 13, wherein said compound is of the formula:

16. (currently amended) The compound of claim 1, according to formula Ie

wherein:

 R^{1} is a member selected from the group consisting of a C_{6} - C_{10} aryl substituted with 0-3 R^{1a} , a 5- to 6-membered monocyclic or 8- to 10-membered bicyclic heteroaryl containing 1-to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R^{1a} ;

each R^{1a} is independently a member selected from the group consisting of H, C_1 - C_3 perfluoroalkyl, C_3 - C_7 cycloalkyl, F, Cl, Br, CN, NO₂, OR ¹⁰, SCH₃, S(=O)CH₃, S(=O)₂R ¹⁰, NR ¹¹R ¹², acetyl, C(=O)OR ¹³, C(=O)NR ¹³R ¹⁴, S(=O)₂NR ¹³R ¹⁴, phenyl substituted with 0-3 R ¹⁵, a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R ¹⁵, a C_3 - C_8 heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said

Inventors: Liu, et al.

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 12

heteroeyele is substituted with 0-2 R^{1e} and is saturated or unsaturated, and a C_1 - C_4 alkyl substituted with 0-2 R^{16} ; and

Ar is phenyl substituted with 0-3 R²⁹, or alternatively, R²⁹ and R⁹ are taken together to form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s) each independently a member selected from the group consisting of N, O and S; wherein said 5- to 7-membered fused heterocyclic ring is substituted with 0-2 R¹⁹.

17. (original) The compound of claim 16, wherein:

 R^2 is a member selected from the group consisting of a C_1 - C_2 alkyl substituted with 1 R^{2a} , and C_1 - C_6 alkyl;

each R^{2a} is independently a member selected from the group consisting of a phenyl substituted with 0-3 R^{15} , and a C_3 - C_8 cycloalkyl substituted with 0-2 R^{19} ; and

 R^5 is a member selected from the group consisting of H, C_3 - C_7 cycloalkyl; a C_1 - C_6 alkyl, wherein said C_1 - C_6 alkyl optionally contains a heteroatom selected from the group consisting of $-O_7$, $-S_7$, $-S(=O)_7$, $-S(=O)_2$ - and $-NR^{17}$ -.

18. (original) The compound of claim 16, wherein said compound is of the formula:

19. (currently amended) The compound of claim 1, according to formula Ia

wherein:

 R^{1a} is a member selected from the group consisting of C_6 - C_{10} aryl substituted with 0-3 R^{1a} , and a 5- to 6-membered monocyclic or 8- to 10-membered bicyclic heteroaryl containing 1 to 4-heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R^{1a} ;

Inventors: Liu, et al.

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 13

each R^{1a} is independently a member selected from the group consisting of H, C_1 - C_3 perfluoroalkyl, C_3 - C_7 cycloalkyl, F, Cl, Br, CN, NO₂, OR ¹⁰, SCH₃, S(=O)CH₃, S(=O)₂R ¹⁰, NR ¹¹R ¹², acetyl, C(=O)OR ¹³, C(=O)NR ¹³R ¹⁴, S(=O)₂NR ¹³R ¹⁴, phenyl substituted with 0-3 R ¹⁵; and a C_1 - C_4 alkyl substituted with 0-2 R ¹⁶;

 R^2 is a member selected from the group consisting of a phenyl substituted with 0-3 R^{15} ; a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} , a C_1 - C_6 alkyl, a C_1 - C_2 alkyl substituted with $1R^{2a}$, and a C_3 - C_7 cycloalkyl substituted with 0-2 R^{19} ;

each R^{2a} is independently a member selected from the group consisting of a C_6 - C_{10} aryl substituted with 0-3 R^{15} ; a 5- to 6-membered monocyclic or 8- to 10-membered bicyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S; wherein said heteroaryl is substituted with 0-3 R^{15} ; a C_3 - C_8 cycloalkyl substituted with 0-2 R^{19} ; and a C_7 - C_{11} bicycloalkyl substituted with 0-2 R^{19} ; and

Ar is phenyl substituted with 0-3 R²⁹, or alternatively, R²⁹ and R⁹ are taken together to form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s) each independently a member selected from the group consisting of N, O and S; wherein said 5- to 7-membered fused heterocyclic ring is substituted with 0-2 R¹⁹.

20. (original) The compound of claim 19, wherein said compound is of the formula:

21-22. (canceled)

23. (currently amended) The compound of claim 1, according to formula Ig:

$$R^{1}-Y-X-N-C \xrightarrow{H} O \xrightarrow{R^{2}} H \xrightarrow{H} O \xrightarrow{H} O \xrightarrow{R^{5}} H$$

Filing Date: March 23, 2004 Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 14

Ig

Ι

wherein:

 R^5 is a member selected from the group consisting of H, C_3 - C_7 cycloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkyne, phenyl substituted with 0-2 R^{15} ; 5—to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} , and a C_1 - C_6 alkyl substituted with 0-2 R^{18} , wherein said C_1 - C_6 alkyl optionally contains a heteroatom selected from the group consisting of $-O_7$, $-S_7$, $-S(=O)_2$ - and $-NR^{17}$ -.

24. (original) The compound of claim 23, according to formula Ih:

- 25. (original) The compound of claim 1, wherein R^9 is H; and Ar is phenyl substituted with 0-3 R^{29} , or alternatively, R^{29} and R^9 are taken together to form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s) each independently a member selected from the group consisting of N, O and S; wherein said 5- to 7-membered fused heterocyclic ring is substituted with 0-2 R^{19} .
 - 26. (canceled)
- 27. (currently amended) A pharmaceutical composition comprising: a the compound of Formula I in claim 1:

or a pharmaceutically acceptable salt <u>and an excipient.</u> or prodrug thereof, wherein:

R⁴ is a member selected from the group consisting of H, C₆-C₁₀ aryl substituted with 0-3 R^{1a}, a 5- to 6 membered monocyclic or 8- to 10 membered bicyclic heteroaryl containing

Application No.: 10/807,613 Inventors: Liu, *et al*. Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 15

1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R^{1a}, a C₃-C₈ cycloalkyl substituted with 0-2 R^{1b}, wherein said C₃-C₈ cycloalkyl is saturated or unsaturated; and a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R^{1e} and is saturated or unsaturated;

each R^{1a} is independently a member selected from the group consisting of H, C₁-C₃ perfluoroalkyl, C₂-C₇ cycloalkyl, F, Cl, Br, CN, NO₂, OR¹⁰, SCH₃, S(=O)CH₃, S(=O)₂R¹⁰, NR¹¹R¹², acetyl, C(=O)OR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴, phenyl substituted with 0-3 R¹⁵, a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R¹⁶ and is saturated or unsaturated, and a C₁-C₄-alkyl substituted with 0-2 R¹⁶;

each R¹⁶ is independently a member selected from the group consisting of H, OH, F, Cl, acetyl, =O, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃ and OCF₃;

each R^{1e} is independently a member selected from the group consisting of H, OH, F, Cl, =O, C₁-C₆ alkyl substituted with 0.2 R¹⁶, C₁-C₆ alkoxy, CF₃, OCF₃, C(=O)R¹⁰, S(=O)₂R¹⁰, tBoc, Cbz; phenyl substituted with 0.3 R¹⁵; a.5 to 6 membered monocyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0.2 R¹⁵;

 R^2 is a member selected from the group consisting of a phenyl substituted with 0-3 R^{15} , a 5- to 6-membered monocyclic heteroaryl containing 1 to 4-heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} , a C_1 - C_6 -alkyl substituted with 0-2 R^{2a} , wherein said C_1 - C_6 -alkyl optionally contains a heteroatom selected from the group consisting of O, S, and $S(=O)_2$, a C_2 - C_6 -alkenyl, a C_2 - C_6 -alkynyl, a C_3 - C_7 -cycloalkyl substituted with 0-2 R^{19} , wherein said C_3 - C_7 -cycloalkyl optionally contains a heteroatom selected from O, S, and $S(=O)_2$, and a C_7 - C_{14} -bicycloalkyl substituted with 0-2 R^{19} ;

each R^{2a} is independently a member selected from the group consisting of a C_6 C_{40} aryl substituted with 0-3 R^{15} , a 5- to 6-membered monocyclic or 8- to 10-membered bicyclic

 Application No.: 10/807,613
 PATENT

 Inventors: Liu, et al.
 P1095US10

Inventors: Liu, et al. Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 16

heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0 3 R¹⁵, a C₃-C₈ eycloalkyl substituted with 0 2 R¹⁹, and a C₇-C₁₁-bicycloalkyl substituted with 0 2 R¹⁹;

R³ is a member selected from the group consisting of H and C₁-C₄ alkyl; subscript n is 0 or 1;

R⁴ is a member selected from the group consisting of H and C₁-C₆-alkyl;
alternatively, R² and R⁴ are taken together to form a C₅-C₇-cycloalkyl substituted with 0-2 R¹⁹;

 R^5 is a member selected from the group consisting of H, C_3 - C_7 -cycloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkyne, phenyl substituted with 0-2 R^{15} ; 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} , a C_1 - C_6 -alkyl substituted with 0-2 R^{18} , wherein said C_1 - C_6 -alkyl optionally contains a heteroatom selected from the group consisting of C_1 - C_2 - C_3 - C_4 - C_6 -alkyl optionally contains a heteroatom selected

Y is a member independently selected from the group consisting of a bond and $-(CR^{20}R^{21})_m$ -W- $(CR^{22}R^{23})_p$ -;

subscript p is 1 or 2.

subscript m is 0 or 1:,

W is a member independently selected from the group consisting of a bond O-S, $S(=O)-S(=O)_2$ and NR-;

X is selected from the group consisting of -C(=O), -OC(=O) $-NR^{24}$ -C(=O) and $-S(=O)_2$.

each of R^6 , $-R^7$, $-R^8$ and Ridependently a member selected from the group consisting of H and C_1 -C -alkyl-

alternatively R⁵ and R dre taken together to form a C 5 Scloalkyl substituted with 0-2 R⁴⁹:

alternatively & and R are taken together to form a 6.7 membered heterocyclic ring containing 1-2 heteroatoms each independently a member selected from the group consisting of N Q and S:

Ar is a member selected from the group consisting of phenyl substituted with 0-3 R²⁹-, and 5- to 6-membered heteroaryl containing 1 to 4-heteroatoms each independently a member

Inventors: Liu, et al. Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 17

selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0.3 R²⁹:

each R^{10} is independently a member selected from the group consisting of H, C_3 - C_4 eyeloalkyl, a C_4 - C_3 perfluoroalkyl, a C_4 - C_4 -alkyl substituted with 0-1 R^{25} , a phenyl substituted with 0-3 R^{15} ; a 5- to 6-membered heteroaryl containing 1-to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} , and a C_3 - C_8 -heterocycle containing 1-to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R^{16} ;

each R¹¹ is independently a member selected from the group consisting of H, ^tBOC, Cbz, C₃-C₈ eyeloalkyl, (C₁-C₆-alkyl)-C(=O)-, (C₁-C₆alkyl)-S(=O)₂- and a C₁-C₆ alkyl; each of R¹², R¹³ and R¹⁴ is independently a member selected from the group consisting of H and C₁-C₄ alkyl;

alternatively, R¹³ and R¹⁴ on the same N atom are taken together to form a C₅-C₇ heterocycle containing 1-2 heteroatoms each independently a member selected from the group consisting of N, O and S;

each R^{15} is independently a member selected from the group consisting of H, OH, F, CI, Br, I, CN, NO₂, COOR 13 , C(=O)NR 13 R 14 , S(=O)₂NR 13 R 14 , acetyl, SCH₃, S(=O)CH₃, S(=O)CH₃, NR 26 R 27 , C₁-C₆ alkoxy, C₁-C₃ perfluoroalkyl, C₁-C₃ perfluoroalkoxy and a C₁-C₆ alkyl;

each R^{16} is independently a member selected from the group consisting of H, OH, $COOR^{13}$, $C(=O)NR^{13}R^{14}$, $S(=O)_2NR^{13}R^{14}$, acetyl, SCH_3 , $S(=O)CH_3$, $S(=O)_2CH_3$, C_1 - C_6 alkoxy, $NR^{26}R^{27}$, a phenyl substituted with 0-3 R^{15} , a 5- to 6-membered heteroaryl containing 1-to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R^{15} , and a C_3 - C_8 heterocycle containing 1-to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R^{15} -and is saturated or unsaturated;

R¹⁷ is a member selected from the group consisting of H and C₁-C₄ alkyl;

each R¹⁸ is independently a member selected from the group consisting of H, OH, F, Cl, CN, NO₂, C(=O)OR³⁰, C(=O)NR¹³R¹⁴, NR¹¹R¹², a C₁-C₃ perfluoroalkyl, a C₁-C₃ perfluoroalkoxy, a phenyl substituted with 0 3 R¹⁵, a 5 to 6 membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O

PATENT P1095US10

Application No.: 10/807,613 Inventors: Liu, et al.

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 18

and S, wherein said heteroaryl is substituted with 0-3 R¹⁵, a C_3 - C_8 heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R¹⁵ and is saturated or unsaturated; and C_3 - C_8 -cycloalkyl;

each R^{19} is a independently a member selected from the group consisting of C_4 - C_4 alkyl, F, Cl and C_4 - C_4 alkoxy, CF_3 and OCF_4 ;

alternatively, two R¹⁹ on the same carbon may be combined to form C₃-C₆-cycloalkyl; each of R²⁰, R²¹, R²² and R²³ is independently a member selected from the group consisting of a bond, H, F, OH, C₁-C₄ alkyl, and C₁-C₂ alkylhydroxy;

alternatively, R^{20} -and R^{21} -or R^{22} -and R^{23} -are taken together to form a C_3 - C_6 eyeloalkyl;

R²⁴ is a member selected from the group consisting of H and C₁-C₄ alkyl;

each R^{25} is independently a member selected from the group consisting of H, C_3 - C_7 eyeloalkyl, a phenyl substituted with 0-3 R^{15} and a 5- to 6-membered heteroaryl containing 1 to 4-heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said 5- to 6-membered heteroaryl is substituted with 0-2 R^{15} ;

each R^{26} is independently a member selected from the group consisting of H, C_4 - C_4 alkyl, $(C_4$ - C_4 alkyl)-C(=O)- and $(C_4$ - C_4 alkyl)- $S(=O)_2$ -;

each R²⁷ is independently a member selected from the group consisting of H and C₁-C₄ alkyl;

alternatively, R²⁶ and R²⁷ on the same N atom are taken together to form a C₅-C₇ heterocycle containing 1-2 heteroatoms each independently a member selected from the group consisting of N, O and S;

each R^{28} is independently a member selected from the group consisting of H, a C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, a phenyl substituted with 0-3 R^{15} , a benzyl substituted with 0-2 R^{15} ;

each R^{29} is independently a member selected from the group consisting of H, F, Cl, Br, I, CN, NO₂, OR^{28} , SR^{28} , $S(=O)R^{28}$, $S(=O)R^{29}$

alternatively, two R²⁹-substituted on adjacent atoms may be combined to form a 5 to 6 membered heterocyclic fused radical, wherein said 5 to 6 membered heterocyclic fused

Filing Date: March 23, 2004 Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 19

radical comprise 1 or 2 heteroatom(s) selected from O, S and N; wherein said 5 to 6 membered heterocyclic fused radical is substituted with 0-1 oxo;

alternatively, R²⁹ and R⁹ are taken together to form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s) each independently a member selected from the group consisting of N, O and S; wherein said 5 to 7-membered fused heterocyclic ring is substituted with 0-2 R¹⁹;

each R³⁰ is independently a member selected from the group consisting of H, C₃-C₄ eycloalkyl, C₄-C₄ alkyl substituted with 0-1 R²⁵, a phenyl substituted with 0-3 R⁴⁵, and a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R⁴⁵; with the proviso that R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are not all hydrogen; and an excepient.

- 28. (currently amended) <u>A pharmaceutical The composition comprising the compound of claim 38 of claim 27, wherein said compound is a member selected from the compounds of Table I.</u>
- 29. (withdrawn) A method of selectively inhibiting cathepsin S activity in a mammal in need thereof, comprising administering to said mammal a therapeutically effective amount of a compound of Formula I:

or a pharmaceutically acceptable salt or prodrug thereof,

I

wherein:

R¹ is a member selected from the group consisting of H, C₆-C₁₀ aryl substituted with 0-3 R^{1a}, a 5- to 6-membered monocyclic or 8- to 10-membered bicyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R^{1a}, a C₃-C₈ cycloalkyl substituted with 0-2 R^{1b}, wherein said C₃-C₈ cycloalkyl is saturated or unsaturated; and a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group

PATENT P1095US10

Application No.: 10/807,613 Inventors: Liu, *et al*. Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 20

consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R^{1c} and is saturated or unsaturated:

each R^{1a} is independently a member selected from the group consisting of H, C_1 - C_3 perfluoroalkyl, C_3 - C_7 cycloalkyl, F, Cl, Br, CN, NO₂, OR^{10} , SCH_3 , $S(=O)CH_3$, $S(=O)_2R^{10}$, $NR^{11}R^{12}$, acetyl, $C(=O)OR^{13}$, $C(=O)NR^{13}R^{14}$, $S(=O)_2NR^{13}R^{14}$, phenyl substituted with 0-3 R^{15} , a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} , a C_3 - C_8 heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R^{16} and is saturated or unsaturated, and a C_1 - C_4 alkyl substituted with 0-2 R^{16} ;

each R^{1b} is independently a member selected from the group consisting of H, OH, F, Cl, acetyl, =O, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, CF_3 and OCF_3 ;

each R^{1c} is independently a member selected from the group consisting of H, OH, F, Cl, =O, C₁-C₆ alkyl substituted with 0-2 R^{16} , C₁-C₆ alkoxy, CF₃, OCF₃, C(=O) R^{10} , S(=O) $_2R^{10}$, tBoc, Cbz; phenyl substituted with 0-3 R^{15} ; a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} ;

 R^2 is a member selected from the group consisting of a phenyl substituted with 0-3 R^{15} , a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} , a C_1 - C_6 alkyl substituted with 0-2 R^{2a} , wherein said C_1 - C_6 alkyl optionally contains a heteroatom selected from the group consisting of $-O_7$, $-S_7$, and $-S(=O)_2$ -, a C_2 - C_6 alkenyl, a C_2 - C_6 alkynyl, a C_3 - C_7 cycloalkyl substituted with 0-2 R^{19} , wherein said C_3 - C_7 cycloalkyl optionally contains a heteroatom selected from $-O_7$, $-S_7$, and $-S(=O)_2$ -, and a C_7 - C_{11} bicycloalkyl substituted with 0-2 R^{19} ;

each R^{2a} is independently a member selected from the group consisting of a C_6 - C_{10} aryl substituted with 0-3 R^{15} , a 5- to 6-membered monocyclic or 8- to 10-membered bicyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R^{15} , a C_3 - C_8 cycloalkyl substituted with 0-2 R^{19} , and a C_7 - C_{11} bicycloalkyl substituted with 0-2 R^{19} ;

R³ is a member selected from the group consisting of H and C₁-C₄ alkyl;

Inventors: Liu, et al.

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 21

subscript n is 0 or 1;

 R^4 is a member selected from the group consisting of H and C_1 - C_6 alkyl; alternatively, R^2 and R^4 are taken together to form a C_5 - C_7 cycloalkyl substituted with 0-2 R^{19} ;

 R^5 is a member selected from the group consisting of H, C_3 - C_7 cycloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkyne, phenyl substituted with 0-2 R^{15} ; 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} , a C_1 - C_6 alkyl substituted with 0-2 R^{18} , wherein said C_1 - C_6 alkyl optionally contains a heteroatom selected from the group consisting of -O-, -S-, -S(=O)-, -S(=O)_2- and -N R^{17} -;

Y is a member independently selected from the group consisting of a bond and $-(CR^{20}R^{21})_m$ -W- $(CR^{22}R^{23})_p$ -;

subscript p is 1 or 2;

subscript m is 0 or 1;

W is a member independently selected from the group consisting of a bond, -O-, -S-, -S(=O)-, -S(=O)₂- and $-NR^{12}$ -;

X is selected from the group consisting of -C(=O)-, -OC(=O)-, -NR 24 C(=O)- and -S(=O)₂-;

each of R^6 , R^7 , R^8 and R^9 is independently a member selected from the group consisting of H and C_1 - C_4 alkyl;

alternatively, R^5 and R^7 are taken together to form a C_5 - C_7 cycloalkyl substituted with 0-2 R^{19} ;

alternatively, R⁵ and R⁹ are taken together to form a 6-7 membered heterocyclic ring containing 1-2 heteroatoms each independently a member selected from the group consisting of N, O and S;

Ar is a member selected from the group consisting of phenyl substituted with 0-3 R^{29} , and 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R^{29} ;

each R^{10} is independently a member selected from the group consisting of H, C_3 - C_7 cycloalkyl, a C_1 - C_3 perfluoroalkyl, a C_1 - C_4 alkyl substituted with 0-1 R^{25} , a phenyl substituted with 0-3 R^{15} ; a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each

PATENT P1095US10

Application No.: 10/807,613 Inventors: Liu, et al.

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 22

independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} , and a C_3 - C_8 heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R^{1c} ;

each R¹¹ is independently a member selected from the group consisting of H, ^tBOC, Cbz, C₃-C₈ cycloalkyl, (C₁-C₆ alkyl)-C(=O)-, (C₁-C₆ alkyl)-S(=O)₂- and a C₁-C₆ alkyl; each of R¹², R¹³ and R¹⁴ is independently a member selected from the group consisting of H and C₁-C₄ alkyl;

alternatively, R^{13} and R^{14} on the same N atom are taken together to form a C_5 - C_7 heterocycle containing 1-2 heteroatoms each independently a member selected from the group consisting of N, O and S;

each R^{15} is independently a member selected from the group consisting of H, OH, F, Cl, Br, I, CN, NO₂, COOR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴, acetyl, -SCH₃, -S(=O)CH₃, -S(=O)₂CH₃, NR²⁶R²⁷, C₁-C₆ alkoxy, C₁-C₃ perfluoroalkyl, C₁-C₃ perfluoroalkoxy and a C₁-C₆ alkyl;

each R¹⁶ is independently a member selected from the group consisting of H, OH, COOR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴, acetyl, -SCH₃, -S(=O)CH₃, -S(=O)₂CH₃, C₁-C₆ alkoxy, NR²⁶R²⁷, a phenyl substituted with 0-3 R¹⁵, a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R¹⁵, and a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R¹⁵ and is saturated or unsaturated;

R¹⁷ is a member selected from the group consisting of H and C₁-C₄ alkyl; each R¹⁸ is independently a member selected from the group consisting of H, OH, F, Cl, CN, NO₂, C(=O)OR³⁰, C(=O)NR¹³R¹⁴, NR¹¹R¹², a C₁-C₃ perfluoroalkyl, a C₁-C₃ perfluoroalkoxy, a phenyl substituted with 0-3 R¹⁵, a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R¹⁵ and is saturated or unsaturated; and C₃-C₈ cycloalkyl;

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 23

each R^{19} is a independently a member selected from the group consisting of C_1 - C_4 alkyl, F, Cl and C_1 - C_4 alkoxy, CF_3 and OCF_3 ;

alternatively, two R^{19} on the same carbon may be combined to form C_3 - C_6 cycloalkyl; each of R^{20} , R^{21} , R^{22} and R^{23} is independently a member selected from the group consisting of a bond, H, F, OH, C_1 - C_4 alkyl, and C_1 - C_3 alkylhydroxy;

alternatively, R^{20} and R^{21} or R^{22} and R^{23} are taken together to form a $C_3\text{-}C_6$ cycloalkyl;

R²⁴ is a member selected from the group consisting of H and C₁-C₄ alkyl;

each R^{25} is independently a member selected from the group consisting of H, C_3 - C_7 cycloalkyl, a phenyl substituted with 0-3 R^{15} and a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said 5- to 6-membered heteroaryl is substituted with 0-2 R^{15} ;

each R^{26} is independently a member selected from the group consisting of H, C_1 - C_4 alkyl, $(C_1$ - C_4 alkyl)-C(=O)- and $(C_1$ - C_4 alkyl)- $S(=O)_2$ -;

each R^{27} is independently a member selected from the group consisting of H and C_1 - C_4 alkyl;

alternatively, R^{26} and R^{27} on the same N atom are taken together to form a C_5 - C_7 heterocycle containing 1-2 heteroatoms each independently a member selected from the group consisting of N, O and S;

each R^{28} is independently a member selected from the group consisting of H, a C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, a phenyl substituted with 0-3 R^{15} , a benzyl substituted with 0-2 R^{15} ;

each R²⁹ is independently a member selected from the group consisting of H, F, Cl, Br, I, CN, NO₂, OR²⁸, SR²⁸, S(=O)R²⁸, S(=O)₂R²⁸, S(=O)₂R¹³R¹⁴, NR²⁶R²⁷, acetyl, C(=O)NR¹³R¹⁴, C(=O)OR¹³, C₁-C₆ alkyl, OCHF₂, SCF₃, OCF₃, -C(=NH)NH₂, and 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S;

alternatively, two R²⁹ substituted on adjacent atoms may be combined to form a 5 to 6 membered heterocyclic fused radical, wherein said 5 to 6 membered heterocyclic fused radical comprise 1 or 2 heteroatom(s) selected from O, S and N; wherein said 5 to 6 membered heterocyclic fused radical is substituted with 0-1 oxo;

alternatively, R²⁹ and R⁹ are taken together to form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s) each independently a member selected from

Inventors: Liu, et al.

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 24

the group consisting of N, O and S; wherein said 5 to 7 membered fused heterocyclic ring is substituted with 0-2 R¹⁹;

P1095US10

each R^{30} is independently a member selected from the group consisting of H, C_3 - C_7 cycloalkyl, C_1 - C_4 alkyl substituted with 0-1 R^{25} , a phenyl substituted with 0-3 R^{15} , and a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R^{15} ; and with the proviso that R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are not all hydrogen.

- 30. (withdrawn) The method of claim 29, wherein the cathepsin S inhibition constant for a compound of Formula I is less than 10 μ M.
- 31. (withdrawn) The method of claim 30, wherein the cathepsin S inhibition constant for a compound of Formula I is less than 1.0 μ M.
- 32. (withdrawn) The method of claim 31, wherein the cathepsin S inhibition constant for a compound of Formula I is less than 0.1 μ M.
- 33. (withdrawn) The method of claim 29, wherein cathepsin S is selectively inhibited in the presence of at least one other cathepsin.
- 34. (withdrawn) The method of claim 33, wherein the inhibition constant of a compound of Formula I for said at least one other cathepsin is at least 10 times greater than a cathepsin S inhibition constant of a compound of Formula I.
- 35. (withdrawn) The method of claim 34, wherein the inhibition constant of a compound of Formula I for said at least one other cathepsin is at least 100 times greater than said cathepsin S inhibition constant of a compound of Formula I.
- 36. (withdrawn) The method of claim 35, wherein the inhibition constant of a compound of Formula I for said at least one other cathepsin is at least 1000 times greater than said cathepsin S inhibition constant of a compound of Formula I.

Application No.: 10/807,613 PATENT Inventors: Liu, et al. P1095US10

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 25

- 37. (withdrawn) The method of claim 29, wherein said compound is a member selected from the compounds of Table I.
- 38. (new) The compound of claim 1, selected from the group consisting of (S)-N-{1-[2-(5-Fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-3-methyl-butyl}-3-methyl-benzamide;
- $N-(S)-\{2-cyclohexyl-1-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-ethyl\}-4-phenoxy-benzamide;$
- (S)-3-Cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-2-[2-(4-methoxy-phenyl)-acetylamino]-propionamide;
- $(S)-N-\{1-[2-(5-Chloro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-3-methyl-butyl\}-3-methyl-benzamide;$
- (S)-N-{3-Cyclohexyl-1-[2-(7-methoxy-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-propyl}-3-methoxy-benzamide;
- (S)-N-{3-Cyclohexyl-1-[2-(6-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-propyl}-3-methoxy-benzamide;
- (S)-N-{3-Cyclohexyl-1-[2-(7-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-propyl}-3-methoxy-benzamide;
- (S)-N-{3-Cyclohexyl-1-[2-(5-cyano-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-propyl}-3-methoxy-benzamide;

Cyclopropanecarboxylic acid (S)-{2-cyclohexyl-1-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-ethyl}-amide;

- $(S)-N-\{3-Cyclohexyl-1-[2-(4-methoxy-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-propyl\}-3-methoxy-benzamide;$
- (S)-N-{3-Cyclohexyl-1-[2-(5-methoxy-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-propyl}-3-methoxy-benzamide;
- (S)-N-{3-Cyclohexyl-1-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-propyl}-3-methoxy-benzamide;
- (S)-N-{3-Cyclohexyl-1-[2-(5-benzyloxy-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-propyl}-3-methoxy-benzamide;
- $N-\{1-(S)-[2-(4-Methoxy-phenylamino)-propylcarbamoyl]-3-methyl-butyl\}-3-methyl-benzamide;$

Application No.: 10/807,613 Inventors: Liu, et al. Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 26

 $N-\{1-(S)-[2-(4-Methoxy-phenylamino)-1-methyl-ethylcarbamoyl]-3-methyl-butyl\}-3-methyl-benzamide;$

 $N-\{1-(S)-[2-(4-Methoxy-phenylamino)-1-(S)-methyl-ethylcarbamoyl]-3-methyl-butyl\}-3-methyl-benzamide;$

 $N-\{1-(S)-[2-(4-Methoxy-phenylamino)-1-(R)-methyl-ethylcarbamoyl]-3-methyl-butyl\}-3-methyl-benzamide;$

N-{2-Cyclohexyl-(1S)-[2-(4-methoxy-phenylamino)-(1R)-methyl-ethylcarbamoyl]-ethyl}-3-methoxy-benzamide;

 $N-\{(1S)-[2-(5-Fluoro-2,3-dihydro-indol-1-yl)-1,1-dimethyl-ethylcarbamoyl]-2-phenyl-ethyl\}-3-methyl-benzamide;$

 $N-\{1-(S)-[1-(R)-Benzyloxymethyl-2-(4-methoxy-phenylamino)-ethylcarbamoyl]-3-methyl-butyl\}-3-methyl-benzamide;$

N-(S)-{[1-(R)-Benzyloxymethyl-2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-phenyl-methyl}-3-methoxy-benzamide;

 $\label{eq:N-[1-(S)-[1-(R)-Benzyloxymethyl-2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-2-(4-fluoro-phenyl)-ethyl]-3-methoxy-benzamide;}$

 $N-\{1-(S)-[(2-Benzyloxy-1-(R)-(5-fluoro-2,3-dihydro-indol-1-ylmethyl)-ethylcarbamoyl]-3-cyclohexyl-propyl\}-3-methoxy-benzamide;$

N-{3-Cyclohexyl-1-(S)-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-1-(R)-hydroxymethylethylcarbamoyl]-propyl}-3-methoxy-benzamide;

 $\label{eq:N-substitute} N-{3-Cyclohexyl-1-(R)-[(S)-2-(5-fluoro-2,3-dihydro-indol-1-yl)-1-(R)-hydroxymethyl-ethylcarbamoyl]-propyl}-3-methoxy-benzamide;$

(S,S)-5-(5-Fluoro-2,3-dihydro-indol-1-yl)-4-[4-methyl-2-(3-methyl-benzoylamino)-pentanoylamino]-pentanoic acid benzyl ester;

(S,S)-5-(5-Fluoro-2,3-dihydro-indol-1-yl)-4-[4-methyl-2-(3-methyl-benzoylamino)-pentanoic acid;

 $(S,S)-N-\{1-[3-Carbamoyl-1-(5-fluoro-2,3-dihydro-indol-1-ylmethyl)-propylcarbamoyl]-3-methyl-butyl\}-3-methyl-benzamide;$

 $(S,S)-N-\{1-[1-(5-Fluoro-2,3-dihydro-indol-1-ylmethyl)-3-ureido-propylcarbamoyl]-3-methyl-butyl\}-3-methyl-benzamide;$

(S,S)-3-[4-Cyclohexyl-2-(3-methoxy-benzoylamino)-butyrylamino]-4-(5-fluoro-2,3-dihydro-indol-1-yl)-butyric acid benzyl ester;

PATENT P1095US10

Application No.: 10/807,613

Inventors: Liu, et al. Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 27

- (S,S)-3-[4-Cyclohexyl-2-(3-methoxy-benzoylamino)-butyrylamino]-4-(5-fluoro-2,3-dihydro-indol-1-yl)-butyric acid;
- $(S,S)-N-\{1-[1-Benzyl-2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-3-cyclohexyl-propyl\}-3-methoxy-benzamide;$
- (S,S)-N-{3-Cyclohexyl-1-[1-(5-fluoro-2,3-dihydro-indol-1-ylmethyl)-3-methyl-butylcarbamoyl]-propyl}-3-methoxy-benzamide;
- $(S,S)-N-\{3-Cyclohexyl-1-[1-(5-fluoro-2,3-dihydro-indol-1-ylmethyl)-2-methyl-propylcarbamoyl]-propyl\}-3-methoxy-benzamide;$
- $(S,S)-N-\{3-Cyclohexyl-1-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-1-phenyl-thylcarbamoyl]-propyl\}-3-methoxy-benzamide;$
- $N-\{1-(S)-[2-(R)-Benzyloxy-1-(R)-(5-fluoro-2,3-dihydro-indol-1-ylmethyl)-propylcarbamoyl]-3-cyclohexyl-propyl\}-3-methoxy-benzamide;$
- $N-\{1-(R)-[1-(R)-Benzylsulfanylmethyl-2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-3-cyclohexyl-propyl\}-3-methoxy-benzamide;$
- (S,S)-[5-[4-Cyclohexyl-2-(3-methoxy-benzoylamino)-butyrylamino]-6-(5-fluoro-2,3-dihydro-indol-1-yl)-hexyl]-carbamic acid benzyl ester;
- $N-\{2-cyclohexyl-1-(S)-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-ethyl\}-2-(2-fluoro-biphenyl-4-yl)-propionamide;$
- N-{2-cyclohexyl-1-(S)-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-ethyl}-2-p-tolyl-propionamide;
- $N-\{2-cyclohexyl-1-(S)-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-ethyl\}-2-o-tolyl-propionamide;$
- $N-\{2-cyclohexyl-1-(S)-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-ethyl\}-2-(4-fluoro-phenyl)-propionamide;$
- 2-(4-Chloro-phenyl)-N-{2-cyclohexyl-1-(S)-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-ethyl}-propionamide;
- $N-\{2-cyclohexyl-1-(S)-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-ethyl\}-2-(R)-phenyl-propionamide;$
- $N-(S)-\{2-cyclohexyl-1-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-ethyl\}-3-methyl-benzamide;$
- $N-(S)-\{2-cyclohexyl-1-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-ethyl\}-4-(methanesulfonylamino-methyl)-benzamide;$

Application No.: 10/807,613 Inventors: Liu, *et al.* Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 28

 $N-(S)-\{2-cyclohexyl-1-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-ethyl\}-3-methanesulfonyl-benzamide;$

 $N-(S)-\{2-cyclohexyl-1-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-ethyl\}-4-methanesulfonylamino-benzamide;$

 $N-\{2-cyclohexyl-1-(S)-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-ethyl\}-2-(4-hydroxy-phenyl)-propionamide;$

4-Cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-2-(S)-(2-(R)-phenyl-propionylamino)-butyramide;

 $N-\{2-cyclohexyl-1-(S)-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-ethyl\}-2-(R)-phenyl-butyramide;$

 $N-\{1-(S)-[1-(R)-Benzyloxymethyl-2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-2-cyclohexyl-ethyl\}-3-methoxy-benzamide;$

N-{2-Cyclohexyl-1-(S)-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-1-(R)-hydroxymethylethylcarbamoyl]-ethyl}-3-methoxy-benzamide;

 $N-\{1-(S)-[1-(R)-Benzyloxymethyl-2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-3,3-dimethyl-butyl\}-3-methoxy-benzamide;$

 $N-\{1-(S)-[2-(5-Fluoro-2,3-dihydro-indol-1-yl)-1-(R)-hydroxymethyl-ethylcarbamoyl]-3,3-dimethyl-butyl\}-3-methoxy-benzamide;$

3-(S)-(2-(S)-Benzyloxycarbonylamino-4,4-dimethyl-pentanoylamino)-4-(5-fluoro-2,3-dihydro-indol-1-yl)-butyric acid tert-butyl ester;

3-(S)-(2-(S)-Benzyloxycarbonylamino-4,4-dimethyl-pentanoylamino)-4-(5-fluoro-2,3-dihydro-indol-1-yl)-butyric acid;

4-(5-Fluoro-2,3-dihydro-indol-1-yl)-3-(S)-[2-(S)-(3-methoxy-benzoylamino)-4,4-dimethyl-pentanoylamino]-butyric acid tert-butyl ester;

3-(S)-[3-Cyclohexyl-2-(S)-(3-methoxy-benzoylamino)-propionylamino]-4-(5-fluoro-2,3-dihydro-indol-1-yl)-butyric acid benzyl ester;

3-(S)-[3-Cyclohexyl-2-(S)-(3-methoxy-benzoylamino)-propionylamino]-4-(5-fluoro-2,3-dihydro-indol-1-yl)-butyric acid;

4-(5-Fluoro-2,3-dihydro-indol-1-yl)-3-(S)-[2-(S)-(3-methoxy-benzoylamino)-4,4-dimethyl-pentanoylamino]-butyric acid ethyl ester;

 $N-\{1-(S)-[2-Cyano-1-(S)-(5-fluoro-2,3-dihydro-indol-1-ylmethyl)-ethylcarbamoyl]-3,3-dimethyl-butyl\}-3-methoxy-benzamide;$

Application No.: 10/807,613 Inventors: Liu, et al. Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 29

 $N-\{1-(S)-[5-Amino-1-(S)-(5-fluoro-2,3-dihydro-indol-1-ylmethyl)-pentylcarbamoyl]-3-cyclohexyl-propyl\}-3-methoxy-benzamide;$

3-(*S*)-(2-(*S*)-Benzyloxycarbonylamino-3-cyclohexyl-propionylamino)-4-(5-fluoro-2,3-dihydro-indol-1-yl)-butyric acid benzyl ester;

 $1-(S)-[1-(R)-Benzyloxymethyl-2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-2-cyclohexyl-ethyl}-carbamic acid benzyl ester;$

N-{3-Cyclohexyl-1-(S)-[2-(3,5-dimethoxy-benzyloxy)-1-(R)-(5-fluoro-2,3-dihydro-indol-1-ylmethyl)-ethylcarbamoyl]-propyl}-3-methoxy-benzamide;

 $4-\{2-(R)-[4-Cyclohexyl-2-(S)-(3-methoxy-benzoylamino)-butyrylamino]-3-(5-fluoro-2,3-dihydro-indol-1-yl)-propoxymethyl\}-benzoic acid methyl ester;$

(S,S)-N-{3-Cyclohexyl-1-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-1-(4-hydroxy-benzyl)-ethylcarbamoyl]-propyl}-3-methoxy-benzamide;

 $\{2\text{-Cyclohexyl-1-}(S)\text{-}[2\text{-}(5\text{-fluoro-}2,3\text{-dihydro-indol-}1\text{-yl})\text{-}1\text{-}(S)\text{-methyl-ethyl}\}$ -carbamic acid benzyl ester;

4-Benzyloxy-N--(R,S)-{[2-(4-amidinophenylamino)-1-(S)-methyl-ethylcarbamoyl]-(2,4-dichloro-phenyl)-methyl}-benzamide;

 $\{1-(S)-[2-(5-Fluoro-2,3-dihydro-indol-1-yl)-1-(S)-methyl-ethylcarbamoyl]-3,3-dimethyl-butyl\}$ -carbamic acid benzyl ester;

 $\label{eq:cyclopropanecarboxylic acid {1-(S)-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-1-(S)-methyl-ethylcarbamoyl]-3,3-dimethyl-butyl}-amide;$

(S,S)-2-(3-Chloro-benzenesulfonylamino)-3-cyclohexyl-N-[1-methyl-2-(4-trifluoromethoxy-phenylamino)-ethyl]-propionamide;

(S,S)-3-Cyclohexyl-N-[1-methyl-2-(4-trifluoromethoxy-phenylamino)-ethyl]-2-(3-trifluoromethoxy-benzenesulfonylamino)-propionamide;

 $N-((S)-(2-(5-fluoroindolin-1-yl)ethylcarbamoyl) (cyclohexyl)\ methyl)-3-methylbenzamide;$

N-((S)-1-(2-(5-fluoroindolin-1-yl)ethylcarbamoyl)-2-(2-chlorophenyl)ethyl)-3-methylbenzamide;

N-((S)-1-(2-(5-fluoroindolin-1-yl)ethylcarbamoyl)-2-(3-chlorophenyl)ethyl)-3-methylbenzamide;

N-((S)-1-(2-(5-fluoroindolin-1-yl)ethylcarbamoyl)-2-(4-chlorophenyl)ethyl)-3-methylbenzamide;

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 30

- (S)-N-{2-Cyclopentyl-1-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethylcarbamoyl]-ethyl}-3-methyl-benzamide;
- N-((S)-1-(2-(5-fluoroindolin-1-yl)ethylcarbamoyl)-3,3-dimethylbutyl)-3-methylbenzamide;
- N-((S)-1-(2-(5-fluoroindolin-1-yl)ethylcarbamoyl)-3-cyclohexylpropyl)-3-methylbenzamide;
- N-((S)-1-(2-(5-fluoroindolin-1-yl)ethylcarbamoyl)-2-phenylethyl)-3-methylbenzamide;
- N-(R,S)-((3-(5-fluoroindolin-1-yl)-1-hydroxypropan-2-(R)-ylcarbamoyl)(2,4-dichlorophenyl)methyl)-3,4-difluorobenzamide;
- N-(S)-((3-(benzyloxy)-1-(5-fluoroindolin-1-yl)propan-2-(R)-ylcarbamoyl)(2,4-dichlorophenyl)methyl)-3,4-difluorobenzamide;
- (R,S)-N-((2-(5-fluoroindolin-1-yl)ethylcarbamoyl)(2,4-dichlorophenyl)methyl)-3-methylbenzamide;
- (S,S)-N-((3-(5-fluoroindolin-1-yl)-1-hydroxypropan-2-ylcarbamoyl)(2,4-dichlorophenyl)methyl)-3,4-difluorobenzamide;
- (S,S)-4-(5-Fluoro-2,3-dihydro-indol-1-yl)-3-[2-(3-methoxy-benzoylamino)-4,4-dimethyl-pentanoylamino]-butyric acid;
- (S)-3-Cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-2-(5-isoxazol-3-yl-thiophene-2-sulfonylamino)-propionamide;
- (S)-2-(3-Biphenyl-4-yl-ureido)-3-cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-propionamide;
- (S)-3-Cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-2-(4-phenoxybenzenesulfonylamino)-propionamide;
- (S)-3-Cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-2-(naphthalene-1-sulfonylamino)-propionamide;
- (S) 3 Cyclohexyl N [2 (5 fluoro 2, 3 dihydro indol 1 yl) ethyl] 2 (4 trifluoromethyl-benzenesulfonylamino) propionamide;
- (S)-3-Cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-2-(4-trifluoromethoxy-benzenesulfonylamino)-propionamide;
- (S)-3-Cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-2-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-propionamide;

Filing Date: March 23, 2004

Response to Office Action mailed December 7, 2006

Date: March 6, 2007

Page 31

- (S)-3-Cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-2-(4'-methoxy-biphenyl-4-sulfonylamino)-propionamide;
- (S)-3-Cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-2-(4-methoxy-benzenesulfonylamino)-propionamide;
- (S)-3-Cyclohexyl-2-(4-difluoromethoxy-benzenesulfonylamino)-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-propionamide;
- (S)-3-Cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-2-phenylmethanesulfonylamino-propionamide;
- (S)-3-Cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-2-(toluene-3-sulfonylamino)-propionamide;
- (S)-3-Cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-2-[4-(4-methoxy-phenoxy)-benzenesulfonylamino]-propionamide;
- (S)-3-Cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-2-(3-methoxy-benzenesulfonylamino)-propionamide;
- (S,S)-3-Cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-1-methyl-ethyl]-2-(toluene-3-sulfonylamino)-propionamide;
- (S,S)-3-[4,4-Dimethyl-2-(toluene-3-sulfonylamino)-pentanoylamino]-4-(5-fluoro-2,3-dihydro-indol-1-yl)-butyric acid tert-butyl ester;
- (S,S)-3-Cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-1-methyl-ethyl]-2-(3-trifluoromethoxy-benzenesulfonylamino)-propionamide;
- (S,S)-2-(3-Chloro-benzenesulfonylamino)-3-cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-1-methyl-ethyl]-propionamide;
- (S,S)-N-{3-Cyclohexyl-1-[1-(5-fluoro-2,3-dihydro-indol-1-ylmethyl)-3-hydroxy-propylcarbamoyl]-propyl}-3-methoxy-benzamide;
- (S,S)-3-[4,4-Dimethyl-2-(toluene-3-sulfonylamino)-pentanoylamino]-4-(5-fluoro-2,3-dihydro-indol-1-yl)-butyric acid;
- (S,S)-2-Benzene sulfonylamino-3-cyclohexyl-N-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-1-methyl-ethyl]-propionamide; and
- (S,S)-4,4-Dimethyl-2-(toluene-3-sulfonylamino)-pentanoic acid [2-(5-fluoro-2,3-dihydro-indol-1-yl)-1-methyl-ethyl]-amide.